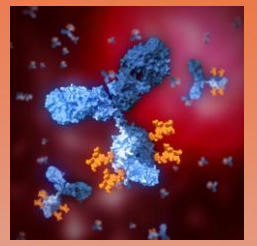
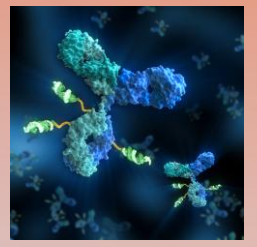
Differences and similarities between Antibody Drug Conjugates (ADCs) & Antibody Oligonucleotide Conjugates (AOCs)





Manjappa Lingaraju (Raju) Gondichatnahalli

Analytical project leader, Novartis Pharma AG, Basel

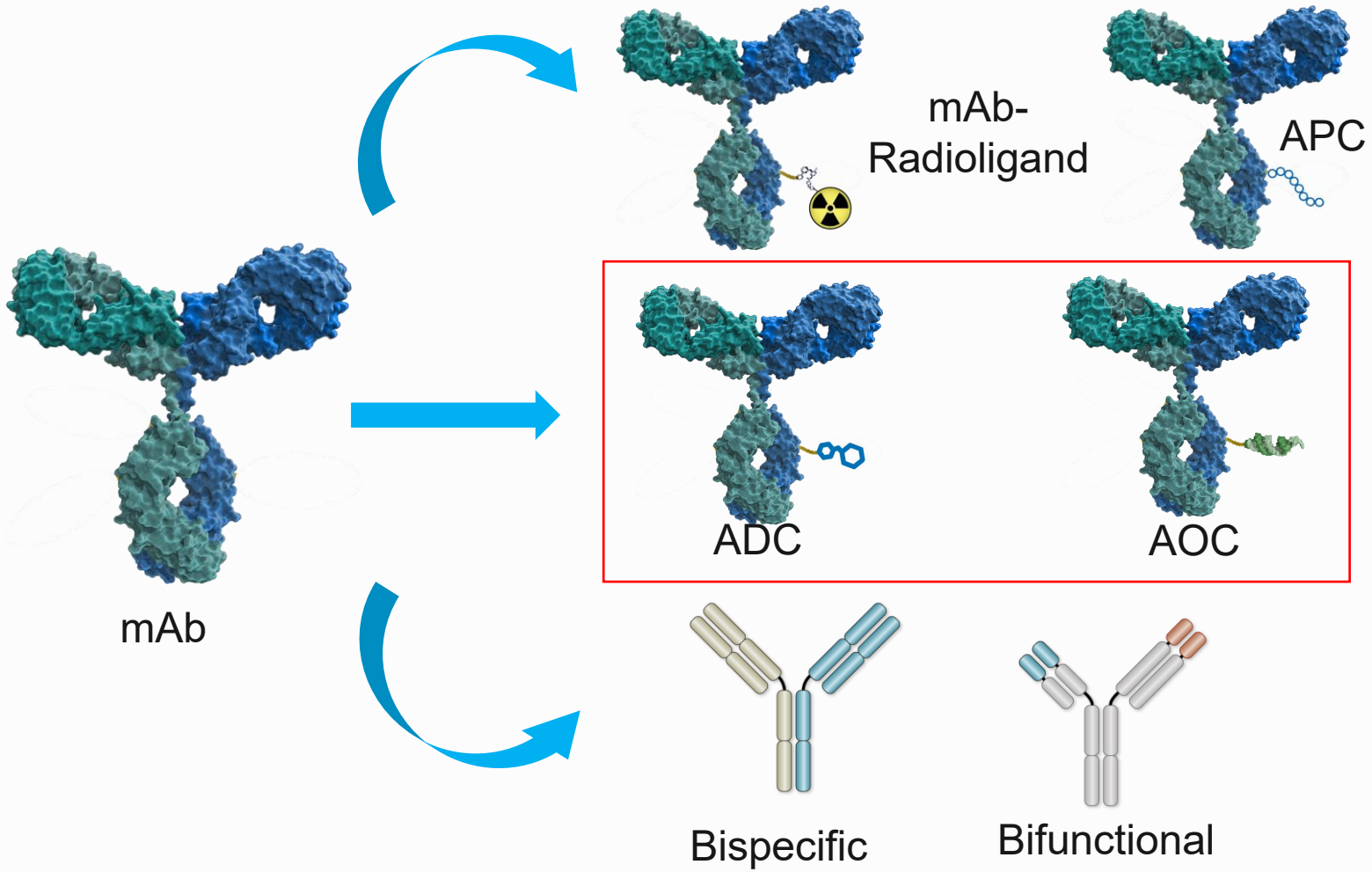
Presented at CASSS CMC Strategy Forum EU 2026 | 23 - 26 June 2026 | Prague, Czech Republic

Agenda

1. Introduction to Bioconjugates, ADCs & AOCs
2. Mechanism of action
3. Design platform ADC & AOC
4. Complexity of CMC and Analytical control strategy; Development challenges
5. Emerging technologies, Platformization trend and Road ahead
6. Therapeutic reach of ADCs and AOCs

Introduction – Antibody x conjugates (AxCs)

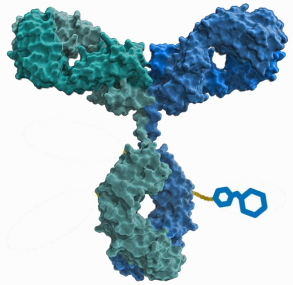
- Diverse possibilities to conjugate mAb with active ingredients



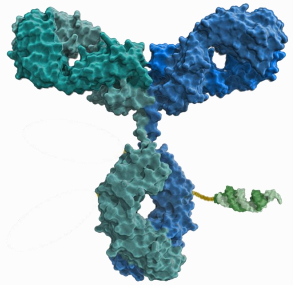
- **Conjugates as Therapeutic Class**
- ADCs: clinically established
- AOCs: emerging modality
- Other formats:
  - Radioligand conjugates
  - Multispecific conjugates
  - Peptide conjugates (APC) etc

Introduction – ADCs and AOCs

- AOCs represent expansion of mAb conjugate platform (e.g. ADC) to address other unmet medical needs
- Core difference: Cytotoxic payload of ADCs vs Gene modulation by AOCs
- AOCs solve key limitation of extrahepatic oligonucleotide delivery -> AOCs represent extension of GalNac conjugated siRNA (oligonucleotide) delivery platform
- Major opportunity to treat diseases, where downregulation and manipulation of genes in a targeted tissue helps the outcome
- Key challenges: CMC and analytical complexity



ADC

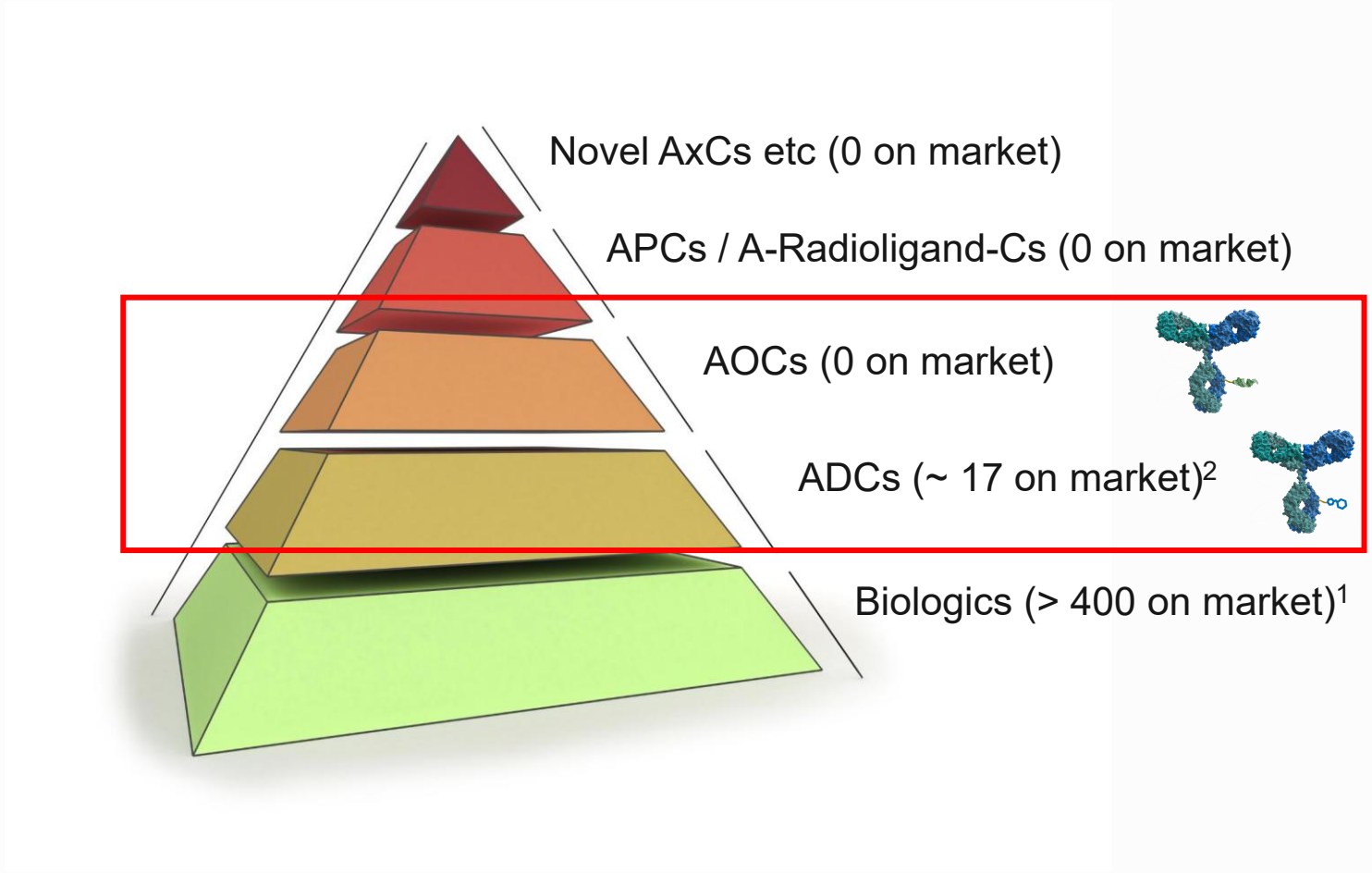


AOC

Introduction – ADCs and AOCs

•ADCs
→ High maturity
- Well-established platform with robust clinical validation
- Incremental innovation (mAb, linkers, payloads, DAR optimization)
- Established Linker-Payload paradigms
- Strong regulatory precedent
- Multiple approved products in market

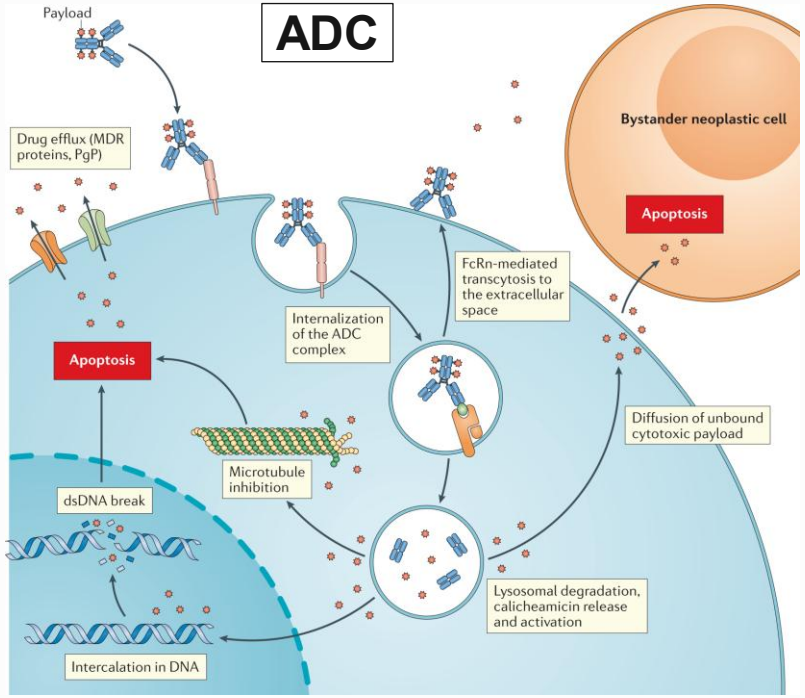
•AOCs
→ Emerging maturity
- Next-generation modality enabling RNA therapeutics delivery
- Delivery-driven Biology
- Unlocks previously undruggable targets (gene expression)
- Still evolving (delivery efficiency, endosomal escape)
- No approved products in market



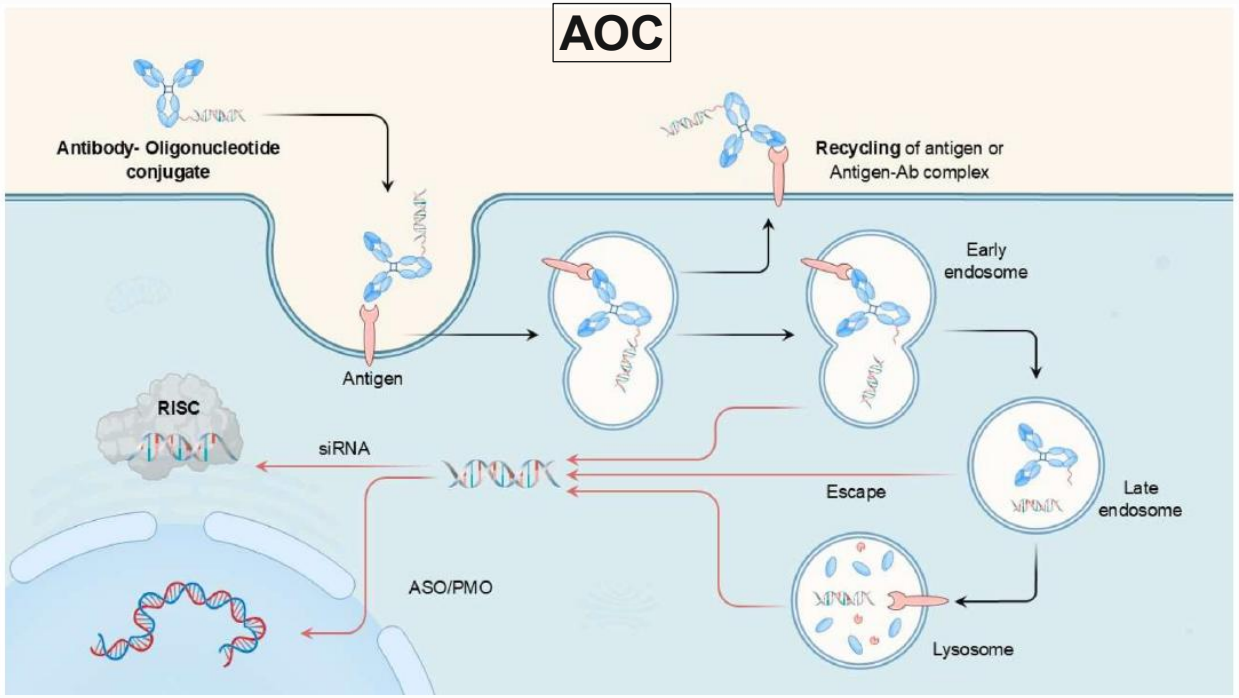
1. Kang & Ji, 2026; Walsch & Walsch 2022
2. Torre & Albericio 2026; Meiyang *et al.*, 2024

Mechanism of action: From cell killing to gene modulation

Feature	ADC	AOC
Payload	Small molecule	siRNA / ASO / PMO
Mechanism	Cell killing	Silencing / exon jumping
Target level	Protein / DNA	RNA
Indication	Oncology	Genetic / CNS -> Oncology



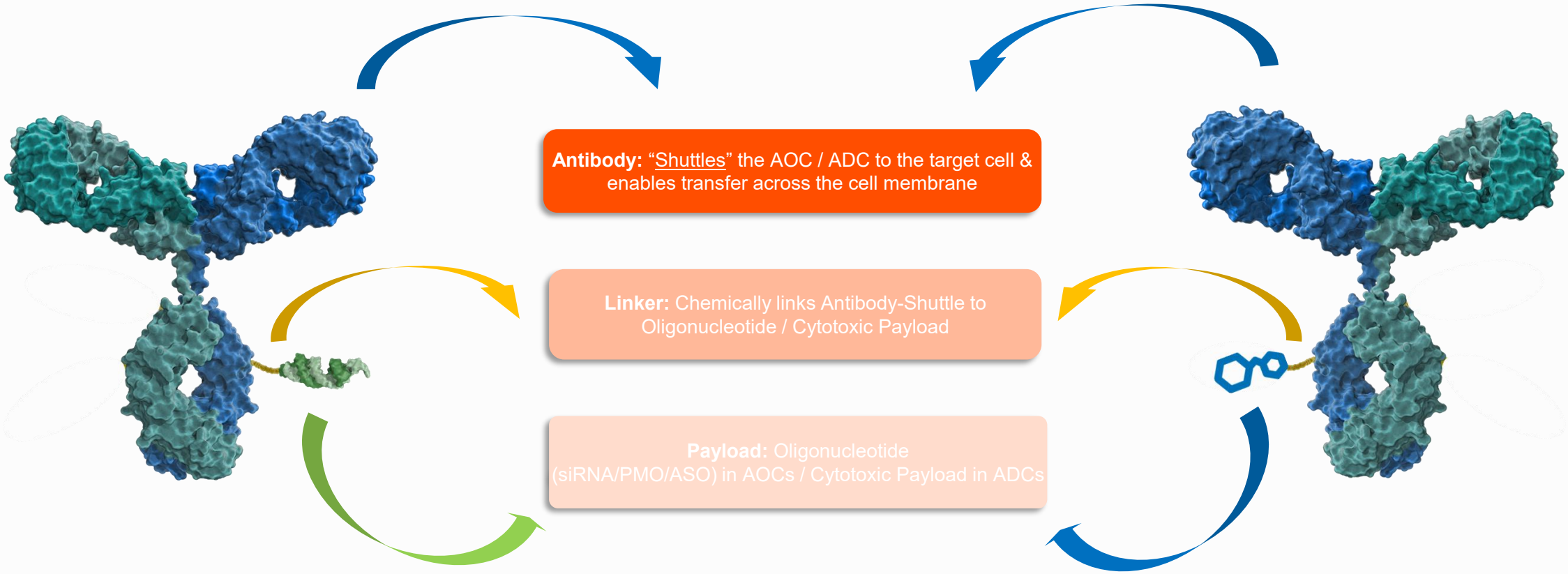
Jabbour E *et al.*, 2021



Meng Li *et al.*, 2025

Design platform: ADC and AOC

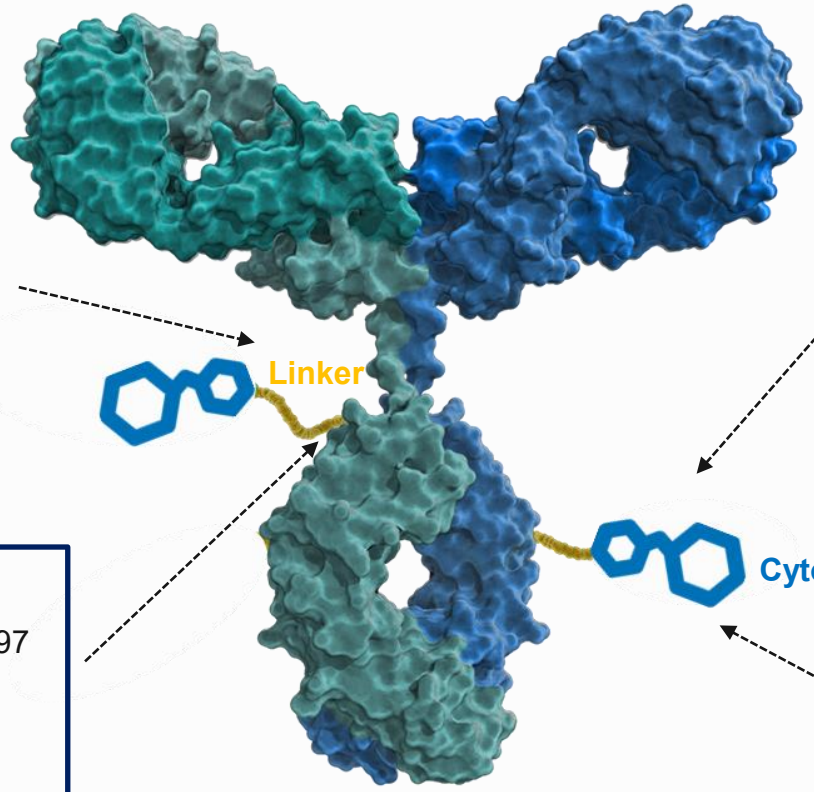
ADCs and AOCs are modular in architecture consisting of 3-elements; a mAb that is conjugated via a linker to one or more cytotoxic payloads / oligonucleotides with the aim of delivering therapy to a target tissue



Design platform: Antibody-Drug-Conjugates (ADCs)

mAb targeting receptors on tumor or cancer cells

Monoclonal Antibody



Linker Selection

- Uncleavable linker SMCC, MC, BisMal etc.
- Cleavable linker: Val-Cit, Val-Ala, (acid-labile, protease clevable, disulphide linkage) etc.

Cytotoxic payload

- Variety of cytotoxic payloads
- Microtubule inhibitors
- DNA synthesis inhibitors
- DNA damaging agents
- Topoisomerase inhibitors
- Cell cycle regulators etc

Antibody conjugation location

- Site specific/native cysteine, Asn-297 (glycan)
- Random: Lysine
- Site-specific conjugation of Lys residues (innovation space)
- Innovations in conjugation chemistry -> can be used for AOCs

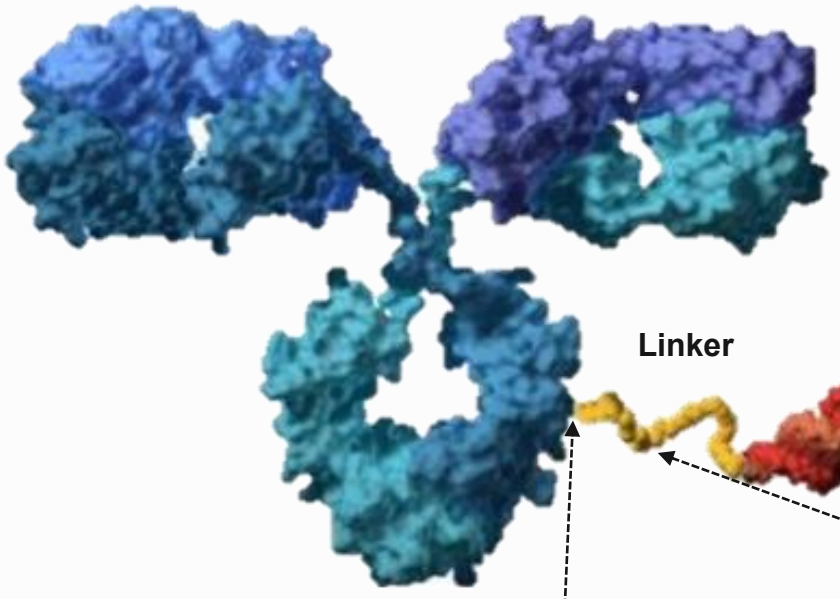
Drug-to-antibody ratio (DAR)

- DAR1,DAR2,DAR3,DAR4. etc

Cochran M *et al.*,2024
Bargh JD *et al.*, 2019

Design platform: Antibody-Oligo-Conjugates (AOCs)

mAb targeting targeting muscle or brain cells



Oligonucleotide chemistry

- siRNA, ASO, PMO
- 2` ribose modification, backbone modification, PEGylation
- Conjugation location: Passenger strand, Guide strand, oligo 3` oder 5`

Oligonucleotide-to-antibody ratio (OAR)

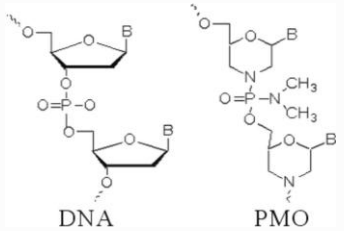
- OAR1,OAR2,OAR3,OAR4. etc

Antibody conjugation location

- Site specific/native cysteine, Asn-297 (glycan)
- Random: lysine

Linker Selection

- Stable linker SMCC, MC, BisMal etc
- Cleavable linker: Val-Cit, Val-Ala etc



PMO: Neutral oligo with phosphorodiamidate backbone with enhanced stability

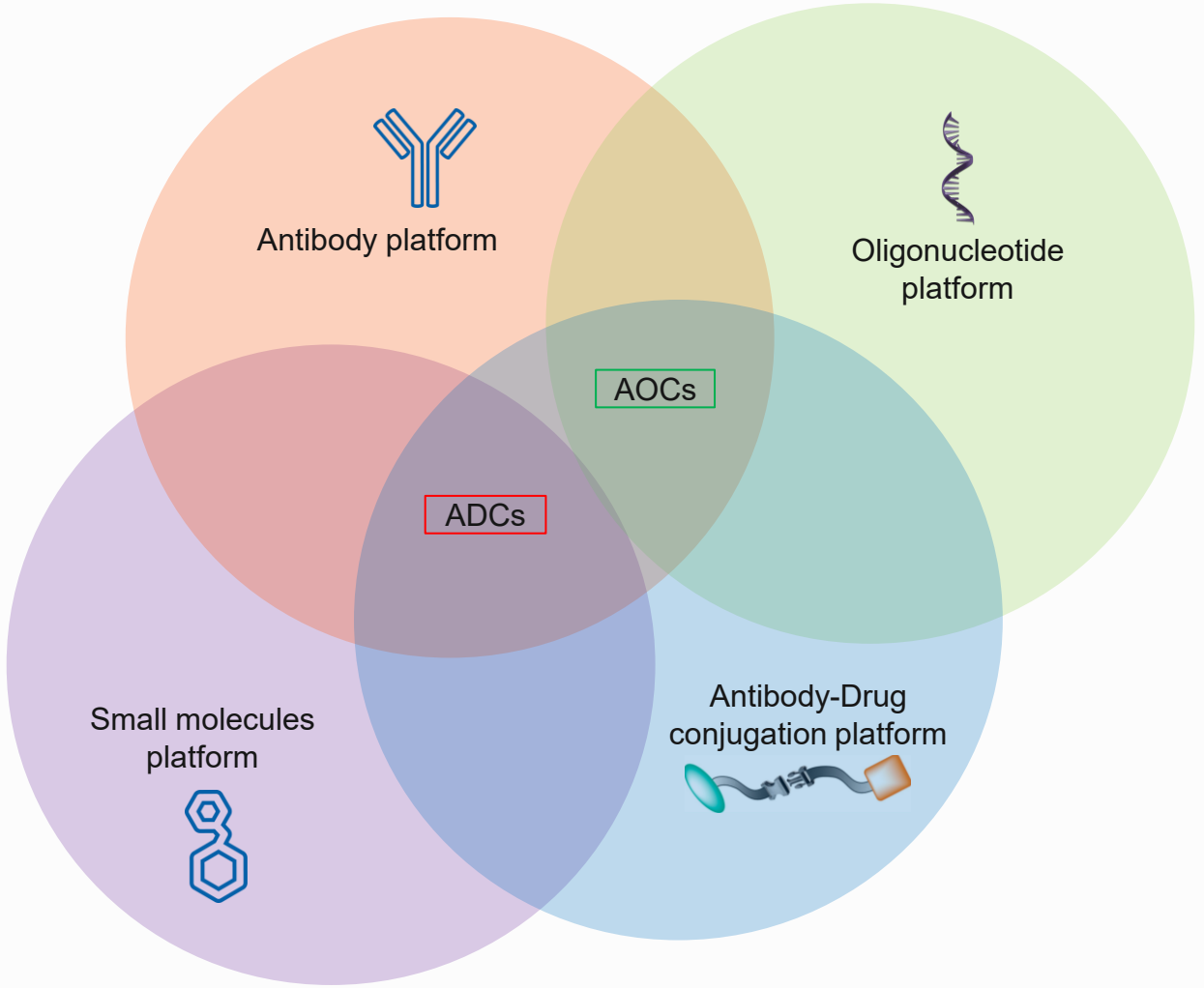
Pharmacological Research 209 (2024) 107469
Cochran M *et al.*,2024
Bargh JD *et al.*, 2019

Platform convergence

Integration of three technologies

- Antibody engineering
- Oligonucleotide therapeutics
- Small molecule therapeutics
- Conjugation chemistry

Platform convergence driven by the alignment of in-house expertise with evolving regulatory expectations and guidelines.



Delivery technologies

ADC:

Tumor targeted intracellular toxin delivery

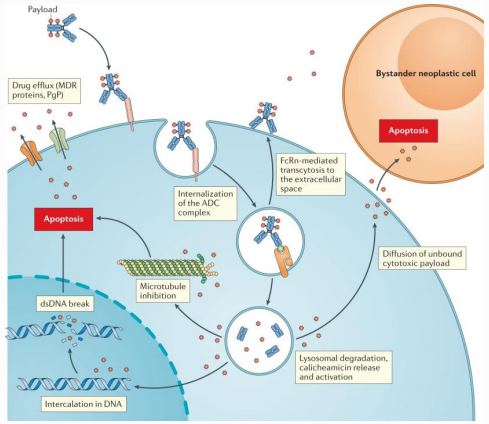
AOC:

Tissue targeted intracellular RNA delivery

Innovations:

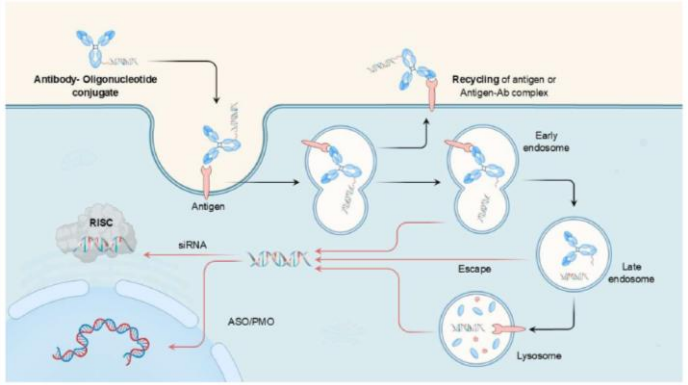
Receptor-mediated uptake
CNS/brain delivery (TfR1)

- ADC



✓ Bystander effect

- AOC



✗ Bystander effect

Linker Design

Linker Function: Different Priorities

- Uncleavable linker SMCC, MC, bisMal (Thioether, Maleimidocapaproyl)
- Cleavable linker: Val-Cit, Val-Ala, (acid-labile, protease clevable, disulphide linkage)

ADC:

Controlled intracellular release

Cleavable linker → breaks → releases drug – bystander effect

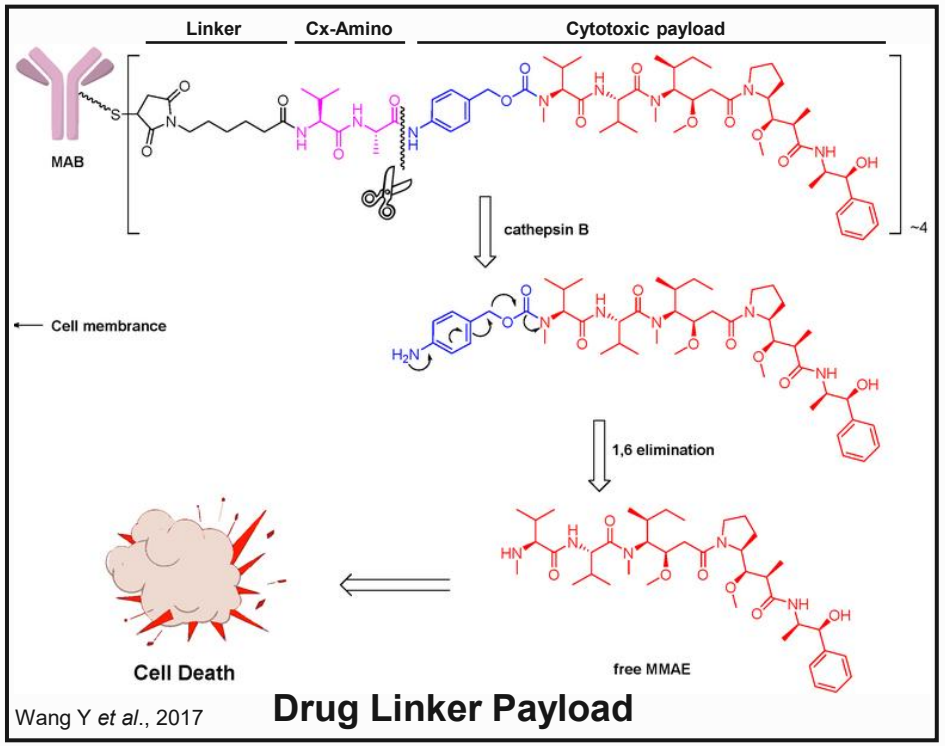
Uncleavable linker → remains stable → delivers drug – less bystander effect

AOC:

Stability + oligo functionality

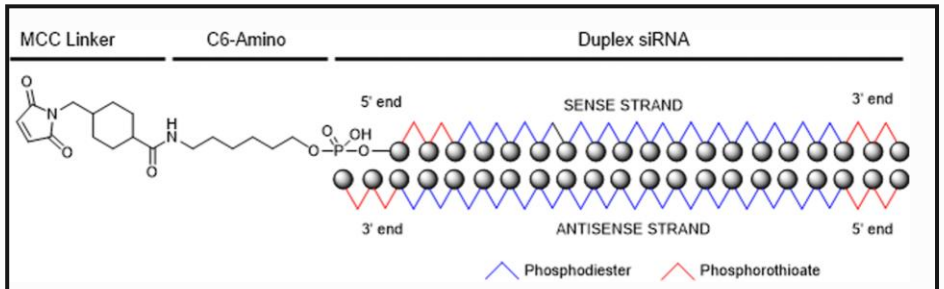
Delivery efficiency

AOC linker → remains stable → delivers oligo – No bystander effect



Wang Y *et al*., 2017

Drug Linker Payload

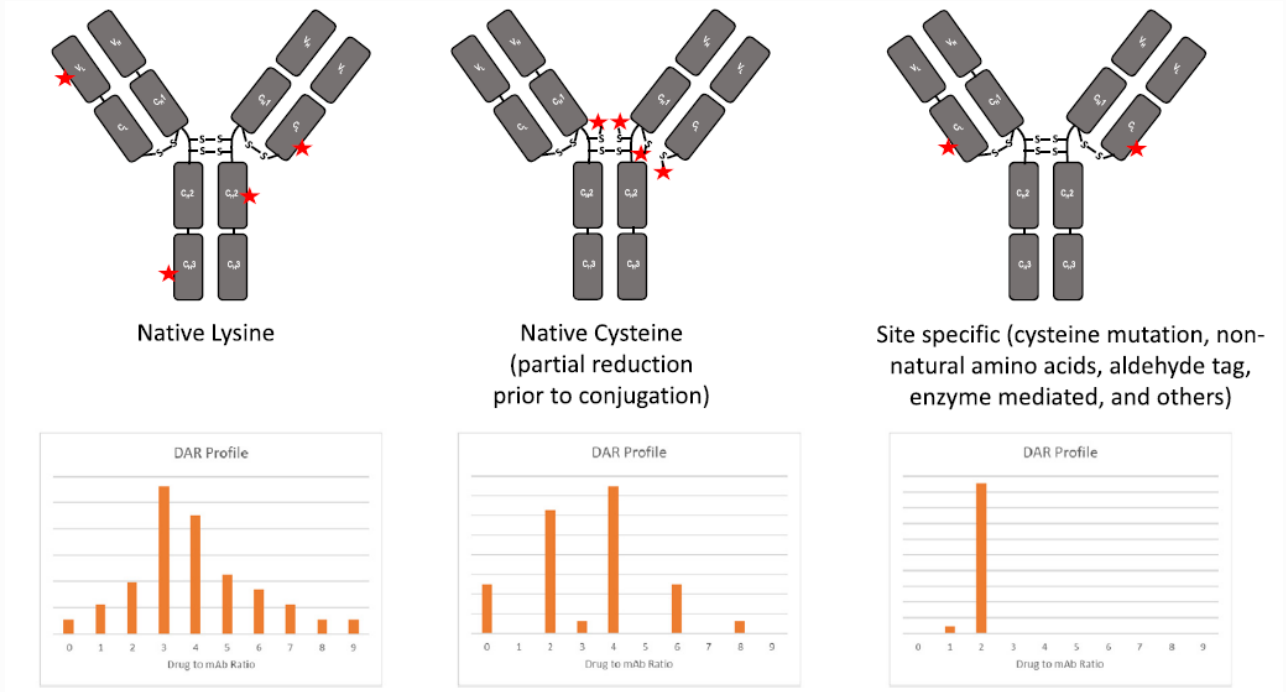


Cochran M *et al*.,2024

Oligo Linker Payload

Conjugation strategy

DAR / OAR profiles differ depending the conjugation strategy and reaction conditions



Higher DAR/OAR -> faster clearance

DAR/OAR – clearance relationship

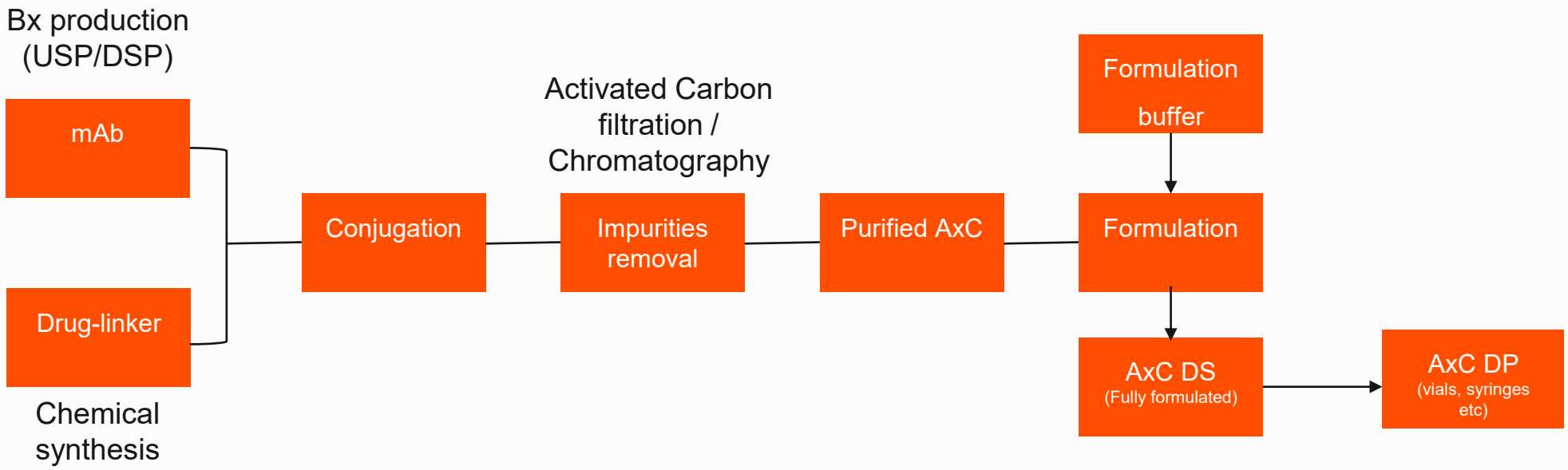
Feature	ADC	AOC
Primary PK driver	Hydrophobicity + FcRn	FcRn + receptor uptake
DAR/OAR effect on hydrophobicity	Strong increase	Minimal to moderate increase
DAR effect on clearance	Strong increased clearance	Moderate increased clearance
High DAR exposure impact	Less exposure	Limited impact on exposure
Optimization goal	Balance clearance vs potency	Maximize delivery while maintaining IgG PK

AOC: DAR – clearance relationship is less established

Bechtold Peters K *et al.*, 2023
Cochran M *et al.*,2024

Conjugation chemistry and reaction conditions play critical role in DAR / OAR distribution

ADC and AOC DS & DP process



Complexity of CMC and Analytical control strategy

ADC:

DAR (Drug ratio)

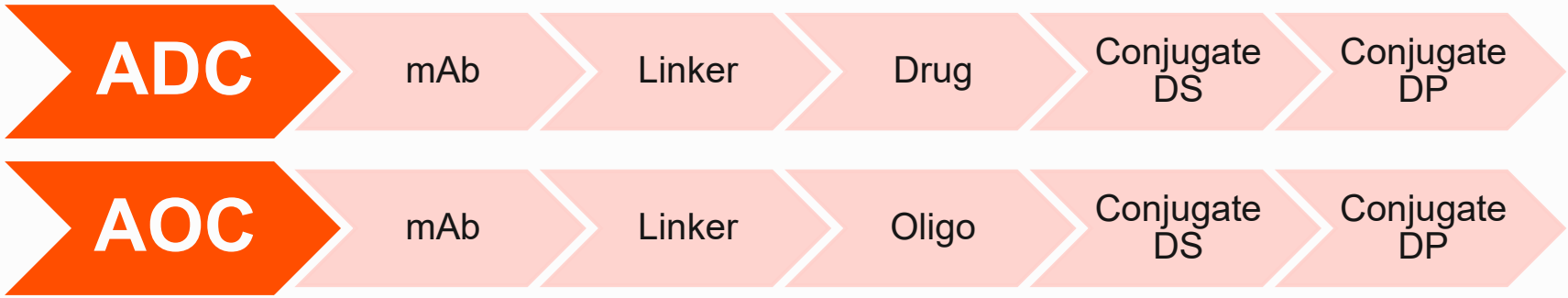
Aggregation

AOC:

OAR (oligo ratio)

Oligo integrity

Hybrid impurity control



- ADC and AOC Analytical control strategy comes with many layers compared to standard mAb
- Non-toxic AOCs do not need same containment as toxic ADCs -> conjugation could be combined with other manufacturing steps
- Small and large molecule related guidelines and concepts (e.g. ICH Q3 / M7 related guide)
- Comparability strategy
- CTD / BLA dossier structure
- Supply / manufacturing network
- Reference standard strategy similar across ADC and AOC (IRS, PRS and SRS/WST)

Analytics for ADCs and AOCs

- Platform methods for Appearance, Excipients, Bioburden/Endotoxin and Content/Quantity
- Content/Quantity by UV is challenging due to complicated calculation of Extinction coefficient
- Comparability strategy is similar to that of mAbs for both ADC and AOCs

Appearance ✓

Quantity ✓

Identity

Purity/Impurities

Potency

Excipients/Surfactants ✓

- ADC: Target binding coupled with other ID tests
- AOC: Standard target binding and related ID tests is challenging and not sufficient (same mAb coupled to different oligos)
- Different identity test is needed e.g. LC-MS

- ADC: Standard purity methods
- AOC: Charge method impacted by negatively charged oligo
- Methods to assess DAR, OAR / free oligo, drug impurities etc.
- AOC: complex CE-SDS profiles for non-specific conjugation strategy

- ADC: Cell based assays are well established
- AOC: Cell-based assay needs to address complex MoA

Development challenges

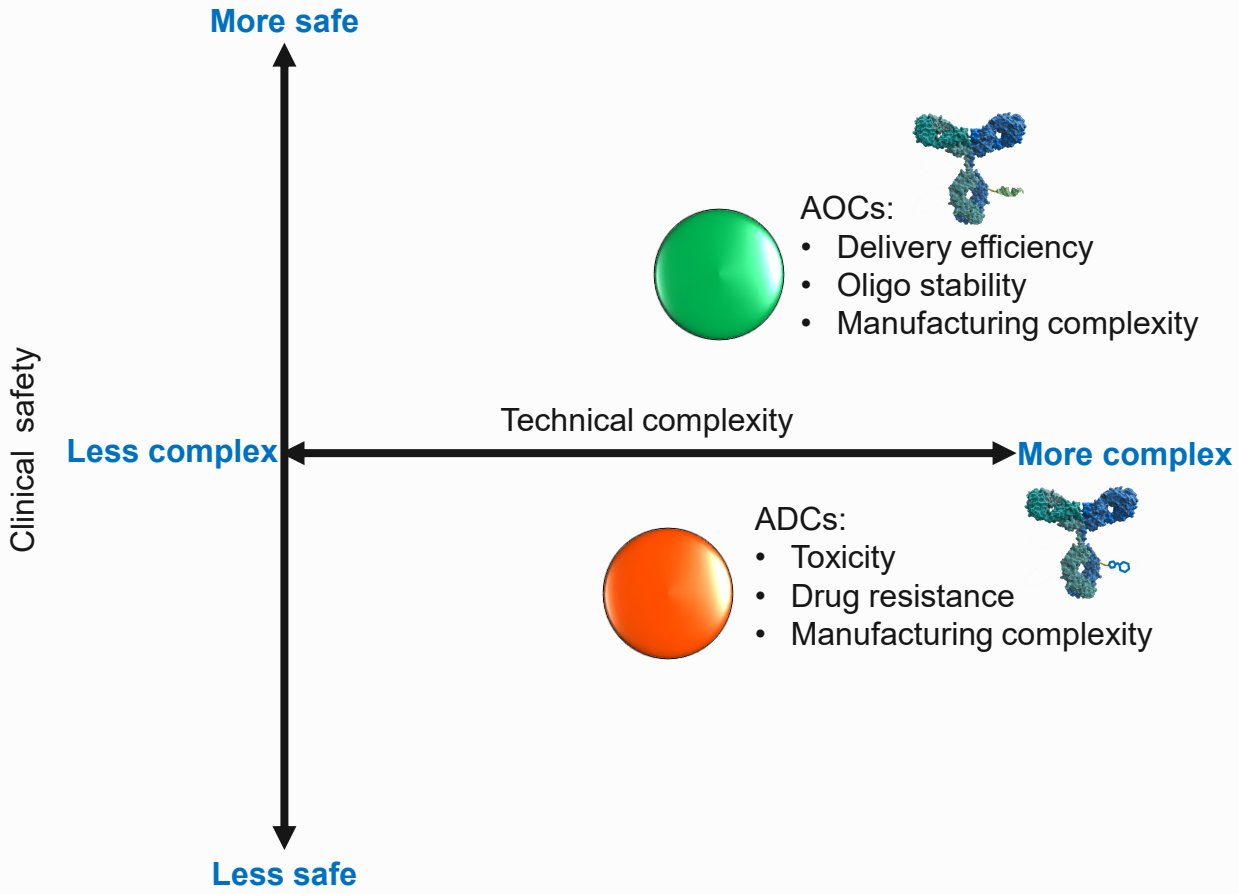
Major Challenges

AOCs

- Delivery efficiency
- Oligo stability
- Manufacturing complexity
- Comparability strategy

ADCs

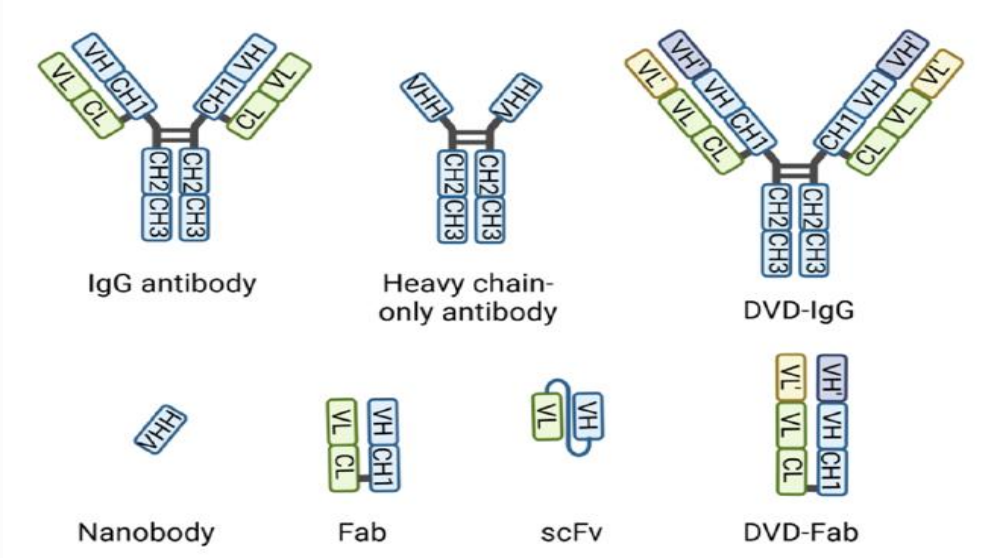
- Toxicity
- Tumor resistance to toxin payload
- Manufacturing complexity
- Comparability strategy



Emerging technologies

Multi specific AxCs:

- Bispecific, Bifunctional or trispecific mAbs
- Antibody fragments
- Advanced drug payload and conjugation chemistry



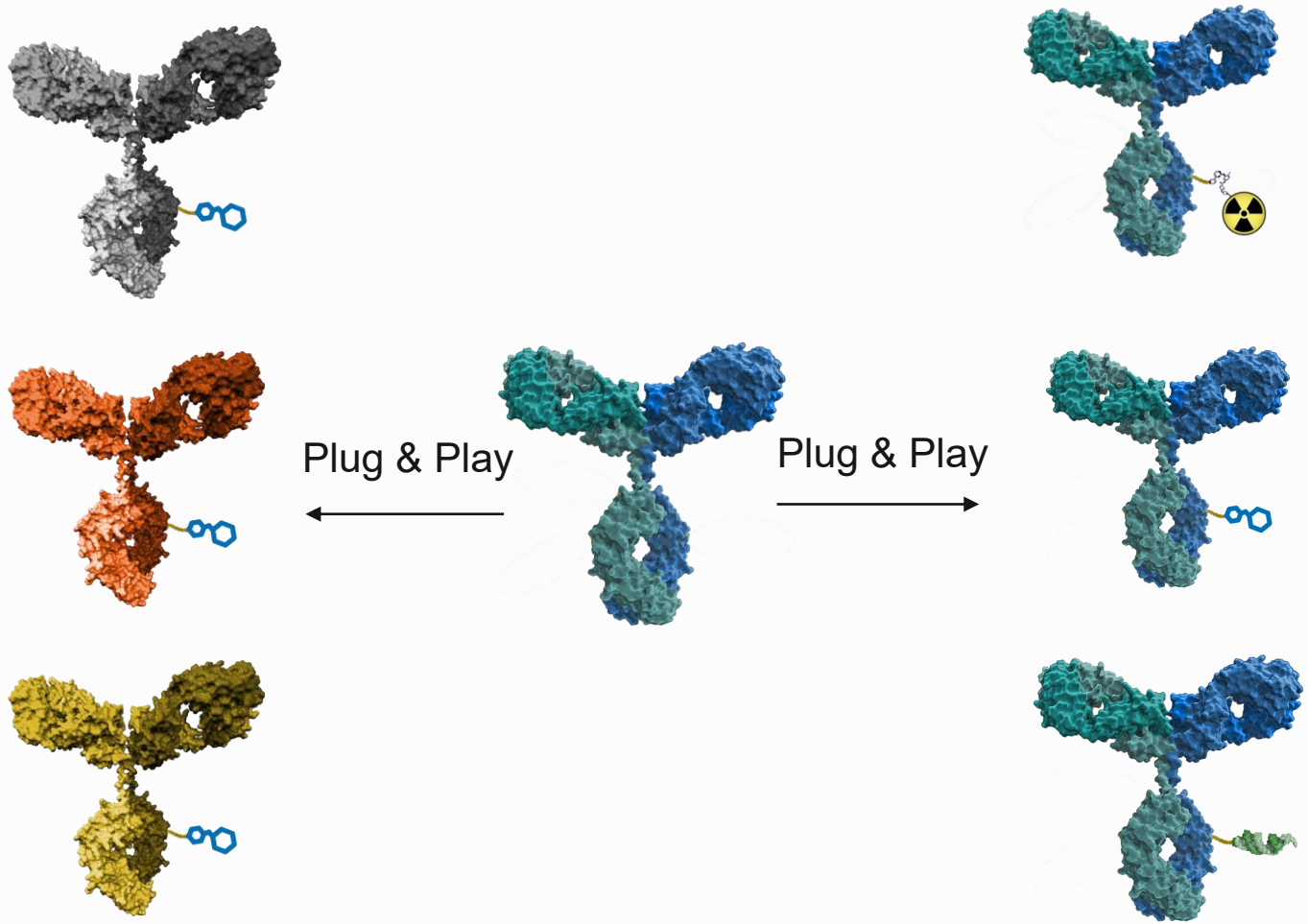
M. Li *et al.*; *2025*

- In principle any Biologics format to achieve tissue specificity

Platformization trend and road ahead

From Drugs to Platforms

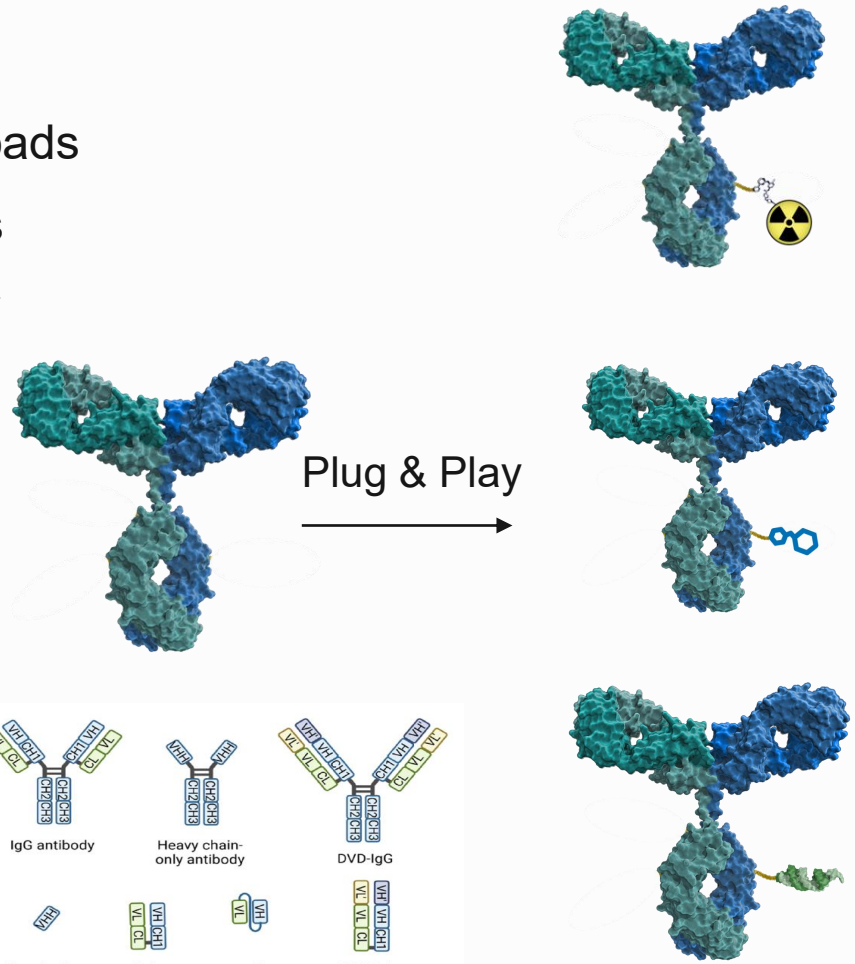
- One antibody → multiple payloads
- One Payload → multiple mAbs
- Modular design → Plug & Play
- Optimization
- Combination therapies
- Hybrid platforms for Antibody multi-conjugates (AxC)



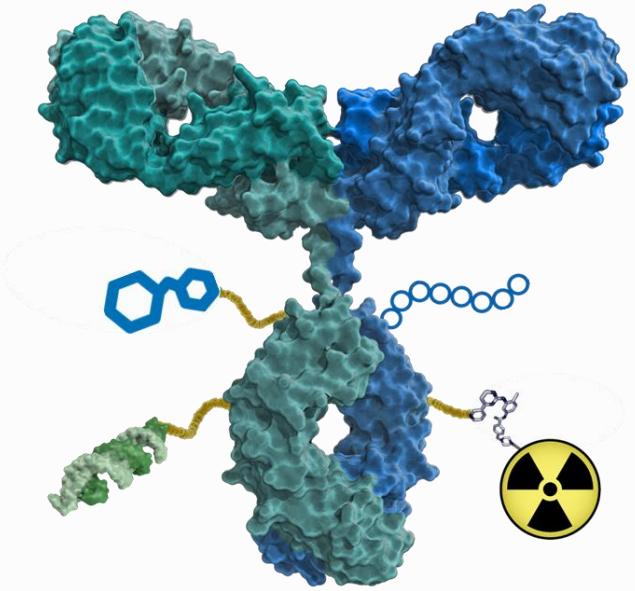
Platformization trend and road ahead

From Drugs to Platforms

- One antibody → multiple payloads
- One Payload → multiple mAbs
- Modular design → Plug & Play
- Optimization
- Combination therapies
- Hybrid platforms for Antibody multi-conjugates (AxC)



M. Li *et al.*; *2025*



Antibody multi-conjugates (AxC)

Therapeutic reach of ADCs and AOCs

ADC:

Oncology dominant

AOC:

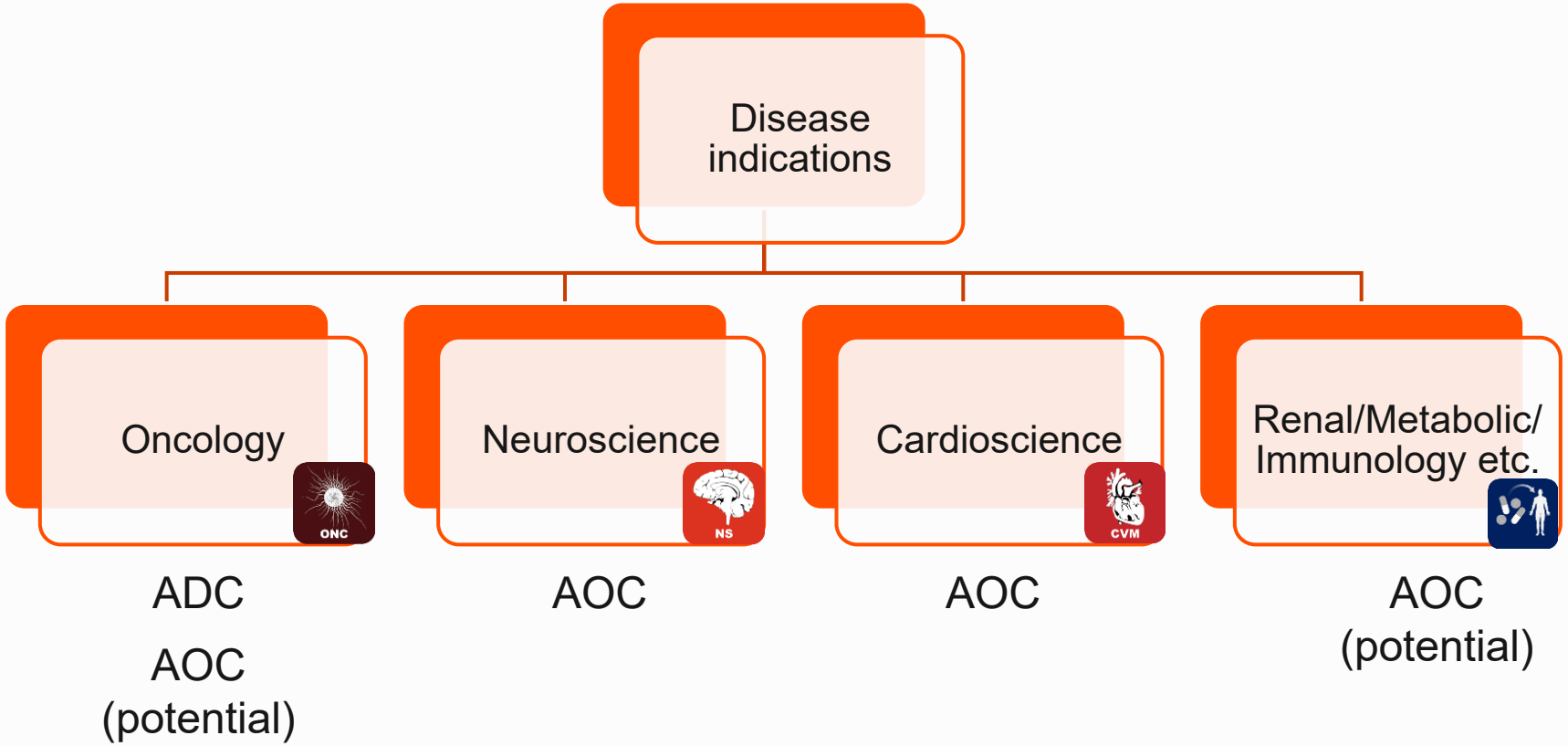
Neuromuscular diseases

CNS (emerging)

Rare diseases

Oncology (future prospects)

Cardiology (future prospects)



AOCs offer a major opportunity to treat any disease, where downregulation of a gene expression or correction of mutated genes to produce functional protein in a specific tissue is needed

Summary

- AOCs and ADCs extend mAb’s paradigm opening new avenues for disease therapy
- Key innovation: Novel tissue targets, Payload/RNA design and delivery
- Increased complexity drives differentiation
- Future: modular conjugate platforms
- How to scale ADC and AOC CMC challenges?
- Categorization of ICH guidelines for AxC and advanced intermediates
- Simplified comparability strategy for drugs of complex architecture
- Defined regulatory pathway for hybrid molecules

Acknowledgments

Thomas Pohl

Andre Mischo

Markus Bluemel

Tim Mollner

Dirk Chelius

Stefanie Siepe

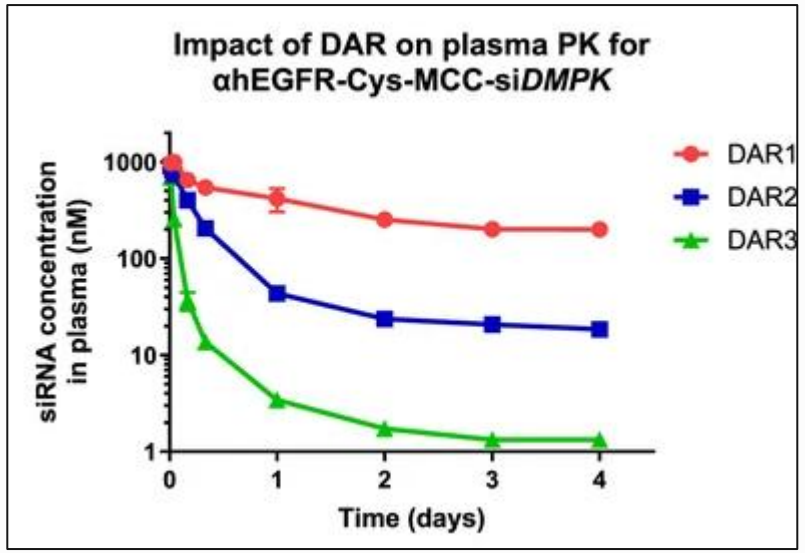
Karoline Bechtold-Peters

Colleagues from TRD Novartis Pharma AG and Avidity Biosciences.

Supplementary Slides

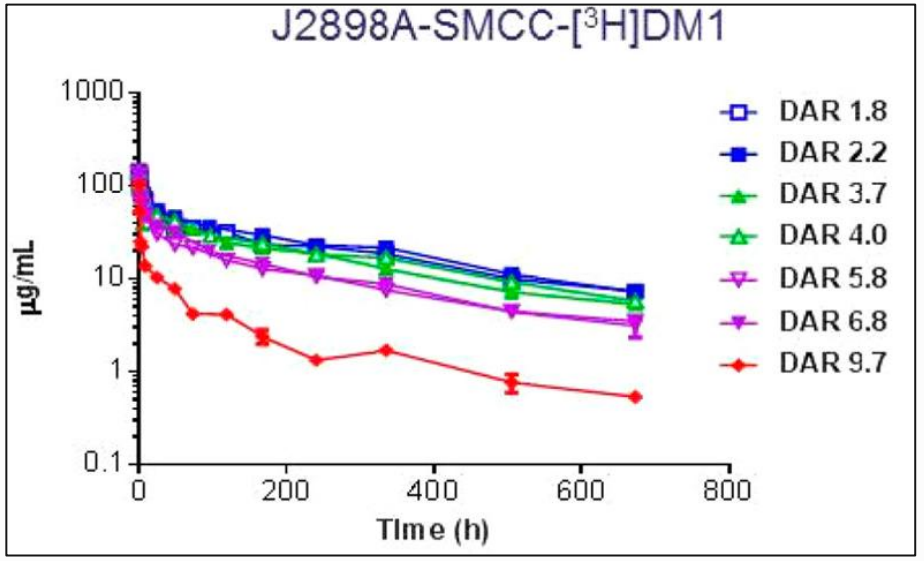
OAR impact on PK

AOC



Cochran M *et al*.,2024

ADC



Sun X *et al*.,2017